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Research report

Interactions between 18-methoxycoronaridine (18-MC) and cocaine: dissociation of behavioural and neurochemical sensitization

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Accepted 18 April 2000

Abstract

The phenomenon of sensitization has been implicated in various aspects of drug addiction. As such, the present study determined the effects of a potential anti-addictive agent, 18-methoxycoronaridine (18-MC; 40 mg/kg, IP, 19 h earlier), on the expression of sensitization following the repeated administration of cocaine (COC; five once daily injections of 15 mg/kg, IP) or saline. The effects of 18-MC on COC metabolism were also assessed. Compared to vehicle controls, 18-MC significantly enhanced the expression of COC-induced locomotion (0, 10, 20 and 40 mg/kg, IP) in chronic COC treated rats only. In both acute and chronic COC rats, 18-MC potentiated the stereotypy induced by higher COC doses (20 and 40 mg/kg, IP). In contrast, 18-MC abolished the sensitized dopamine (DA) response in the nucleus accumbens (NAC) to COC (20 mg/kg), without altering the DA response of acute COC rats. None of the interactions between 18-MC and COC appear to be related to alterations in COC metabolism as no effect of 18-MC pretreatment was observed on extracellular levels of COC or two of its metabolites, benzoylecgonine and norcocaine. From the present findings, it is concluded that the enhancement of COC-induced behaviour produced by 18-MC pretreatment is independent of effects on either COC pharmacokinetics or COC-induced alterations in DA transmission. However, given that 18-MC decreases the self-administration of COC in laboratory animals, it is proposed that the anti-addictive efficacy of 18-MC might be related to an ability to selectively block the expression of sensitized extracellular levels of DA in the NAC in rats with previous COC experience. © 2000 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behavior

Topic: Drugs of abuse: cocaine

Keywords: 18-Methoxycoronaridine (18-MC); Cocaine; Sensitization; Locomotor activity; Dopamine; Drug addiction

1. Introduction

18-Methoxycoronaridine (18-MC) is a synthetic *iboga* alkaloid congener derived from the putative anti-addictive drug ibogaine (IBO). Consistent with its anti-addictive potential, 18-MC effectively decreases morphine, cocaine, ethanol and nicotine self-administration in laboratory animals and attenuates acute signs of morphine withdrawal in physically dependent rats (for reviews [21,22]). Importantly, at least in preclinical studies, 18-MC exerts little to none of the side effects associated with IBO (for

reviews, [21,22]). Thus, 18-MC may be a viable pharmacotherapy for the treatment of addiction [19]. The neural mechanism(s) mediating the anti-addictive effects of IBO and related agents are unclear. However, similar to other *iboga* agents that decrease self-administration, 18-MC decreases extracellular levels of dopamine (DA) in the nucleus accumbens (NAC) (for reviews [20–22]). This action has been proposed to underlie the effects of potential anti-addictive compounds on the reinforcing or incentive motivational properties of abused drugs (e.g. [3,16,28,39,52]).

To better understand the mechanisms through which IBO and 18-MC might exert their putative anti-addictive effects, a series of studies conducted by this laboratory has focused on characterizing and comparing the *in vivo*

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interactions between these *iboga* agents and several addictive drugs. 18-MC mimics the effects of both IBO and noribogaine on the locomotion produced by an acute injection of COC; at pretreatment intervals of 1 and 19 h, all three *iboga* agents attenuate and potentiate, respectively, COC-induced locomotor activation [32]. At least in the case of IBO (19 h earlier), the locomotor effects appear to be related to an enhancement of the COC-induced increase in extracellular DA in both the striatum and NAC [30]. The similar behavioural effects of 18-MC and IBO suggested that 18-MC might also enhance the DAergic effects of acute COC. However, preliminary studies demonstrated that 18-MC does not alter the increase in DA in either the shell of the NAC or the dorsolateral striatum produced by an acute injection of COC [21]. Thus, it appears that 18-MC may alter acute COC-induced locomotor activity via actions at some site(s) downstream of the midbrain DA neurons.

The effects of IBO on drug-induced behaviour can be greater when animals have a previous drug history [4,35,43–46]. In contrast, 18-MC appears to produce differential effects on the expression of morphine-induced locomotion depending upon the prior morphine experience of the animal; in a recent study, 18-MC increased the potency of morphine to induce locomotor activation in acute morphine-treated rats, but blocked the expression of locomotor sensitization in rats repeatedly administered morphine [48]. This latter effect might be attributable to an 18-MC-induced blockade of DA sensitization in the NAC [48]. Thus, the effects of 18-MC pretreatment on the dose–response relationship for COC might also depend on the previous COC history of the animal and involve a specific interaction of 18-MC with sensitized DA transmission in the NAC.

To test this possibility, the present study determined the interactions between 18-MC and COC in rats treated either acutely or repeatedly with COC. The effects of 18-MC pretreatment were assessed in two behavioural experiments, one for locomotion and the other for stereotypy. As previous studies indicated that 18-MC's effects on COC-induced behaviour may be separable from the effects of this agent on COC-induced alterations in accumbal DA transmission, concurrent measurements of extracellular DA in the NAC and of stereotypy were also made in a third experiment. Because the behavioural enhancing effects of 18-MC might have been related to a pharmacokinetic interaction with COC, brain levels of COC and two of its major metabolites, benzoylecgonine (BE) and norcocaine (NorCOC), were also determined.

2. Materials and methods

2.1. Subjects

Consistent with previous reports from our laboratory

(e.g. [43,45–48,56]), subjects were naïve female Sprague–Dawley rats (Taconic, Germantown, NY, USA), weighing 200–225 g (behavioural experiments) or 250–275 g (microdialysis experiment). Females are used exclusively in our sensitization studies as they reliably show more robust behavioural responses to stimulants than do males (e.g. [38]). All animals were housed in polyurethane cages in a colony room controlled for temperature and humidity, maintained on a normal light–dark cycle (lights on/off at 0700 h/1900 h). Food and water were available *ad libitum*.

2.2. Drugs

Cocaine HCl (Sigma, St. Louis, MO) was dissolved in 0.9% saline and injected intraperitoneally (IP) at a volume of 1.0 ml/kg. COC was administered at a dose of 15 mg/kg for the chronic treatment phase of the study and doses of 0, 10, 20 or 40 mg/kg in the tests for sensitization. 18-MC HCl (Albany Molecular Research, Albany, NY, USA), was dissolved in phosphate buffer (VEH; pH=6) and injected IP at a concentration of 20 mg/ml (volume=2 ml/kg).

2.3. Locomotor activity

Eighty-four rats were randomly assigned to groups which received five once daily injections of either COC (15 mg/kg, IP) or SAL. Locomotion was studied in cylindrical (60 cm) photocell activity cages with three intersecting light beams. The photocells were located equidistantly from each other around the circumference of the cage, 3 cm above the floor. Each time a light beam was broken a single activity count was recorded by a 386 PC computer with Med Associates software. To reduce the probability of misinterpreting repetitive movements or movements in front of a photocell as locomotion, single activity counts were recorded by the computer only if two light beams were broken in succession. As described previously [45], animals were habituated to the activity cages for 30 min following an injection of saline (SAL) on each injection day. Following the fifth repeated treatment injection, animals were withdrawn from treatment for 2 weeks. On the last day of withdrawal, rats were randomly assigned to receive a pretreatment injection of either 18-MC (40 mg/kg, IP) or VEH. Nineteen hours later, a dose–response test for sensitization was conducted. On this test, rats received one of four COC doses (0, 10, 20 or 40 mg/kg; $n=5-6$) and locomotor behaviour was monitored for 2 h. Again, a 30 min habituation session preceded the dose–response test.

2.4. Stereotypy

Forty-eight rats were randomly assigned to receive chronic treatment as described above. Stereotypy was observed in clear, ventilated, cylindrical (30 cm) Plexiglas

cages with wire mesh floors. Clear Plexiglas lids were placed on top of the cages to prevent escape of the animals during the injection sessions. Food and water were not available during injection sessions. A behavioural intensity rating scale, adapted from Kalivas et al. [25], was used to quantify the expression of stereotypy by the animals during the injection sessions (see Table 1). Rats were observed for 30 s, at repeated intervals, beginning immediately following injection until the completion of the session. As in the study of locomotor activity, each repeated treatment session was preceded by a 30 min SAL habituation session. Animals were withdrawn from repeated treatment for 2 weeks, pretreated with either 40 mg/kg 18-MC or VEH and then, 19 h later, tested for the expression of stereotypy in response to either 20 or 40 mg/kg (IP) COC. Observations were made either every 15 min for the habituation sessions (total of three observation periods) or every 20 min for the COC injection sessions (total of either six or nine observation periods for chronic treatment and test days, respectively). Rats were given a single score for each 30 s observation period. The observer was blind to the pretreatment of the animals on test days.

2.5. *In vivo* microdialysis

Under pentobarbital anesthesia (50 mg/kg, IP), 25 rats were stereotaxically implanted with two microdialysis guide cannulae (CMA 8309010; Acton, MA) aimed bilaterally, at an angle of 14°, over the nucleus accumbens. The coordinates were chosen such that, when inserted, the tips of the dialysis probes (V, −8.8 mm from the surface of the skull) were located in the medial portion of the shell area of the NAC (AP, +1.6 mm and L, ±3.0 mm) [34]. Animals were monitored for proper recovery but otherwise left undisturbed for 1 day after surgery; chronic COC/SAL treatment then began as described above. On each of the chronic treatment days, rats were transported to the experimental room in their home cages (approximately 13:00 h), injected with either COC (15 mg/kg, IP) or SAL, and returned immediately to their home cages. Home cages were placed on shelves either above, or below, the microdialysis chambers for 3 h, at the end of which time,

rats were returned to the colony room. This procedure was followed to allow for the formation of COC-context associations shown to promote the expression of DA sensitization on test day [41]. As in the behavioural studies, rats were withdrawn from repeated treatment for 2 weeks. The afternoon prior to test day, rats were briefly anesthetized with Brevital (45 mg/kg, IP) and two dialysis probes (CMA 8309502) were inserted through the guide cannulae on each side of the head. Artificial CSF (146 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl₂ and 1.0 mM MgCl₂) was delivered by a Harvard syringe pump at a flow rate of 1 µl/min. Collection of perfusates began the next day (11:00 h). Twenty-min fractions were collected in vials containing 2.0 µl of 1.1 M perchloric acid solution (containing 50 mg/l EDTA and 50 mg/l sodium metabisulfite). After 2 h of baseline collections, the rats received their test injection of COC (20 mg/kg, IP) (13:00 h). The collection of dialysate samples was then continued for 3 h. During the microdialysis session, the behaviour of the animals was rated as described above to provide behavioural correlates for the neurochemical and COC metabolic effects of pretreatment.

2.6. Behavioural scoring during microdialysis

As a behavioural correlate of the changes in extracellular levels of DA, COC, or their respective metabolites, the stereotypic behaviour of the rats were scored during the microdialysis experiment. Behaviour was rated as described above (see Stereotypy) with the following exceptions: sampling of behaviour occurred every 20 min, beginning at 1 h prior to COC injection (baseline behaviour) and ending 3 h after COC administration. Scoring was performed during the 30 s immediately after dialysate collection. In this study, the experimenter was not blind to the pretreatment of the animals.

2.7. Histology

Upon completion of the microdialysis experiment, rats were sacrificed by an overdose of pentobarbital, their brains removed, frozen and sliced (40 µm coronal sec-

Table 1

Rats were given a single score for each 30 s interval according to the following behavioural rating scale (adapted from [25])

Score	Behaviour(s) observed
1	Asleep or still
2	Inactive, grooming or mild licking
3	Locomotion (all four feet move in 30 s), rearing or sniffing
4	Any combination of two of locomotion, rearing or sniffing
5	Continuous sniffing for 30 s without locomotion or rearing
6	Continuous sniffing for 30 s with locomotion or rearing
7	Patterned sniffing for 15 s
8	Patterned sniffing for 30 s
9	Continuous gnawing or focused grooming ('skin-picking'-like behaviour)
10	Bizarre diskinctic movements or seizures

tions) in a cryostat. The tracks left by the probes were identified and their exact positions determined by reference to the atlas of Paxinos and Watson [34]. Only the dialysates of animals whose tracks were within 0.5 mm of the correct placement within the shell of the NAC were analyzed for catecholamines. Only data from animals whose tracks were placed appropriately in the NAC were presented in this paper. For the COC assay, dialysates were analyzed regardless of placement as an index of brain COC metabolism.

2.8. Catecholamine assay

Dialysate samples were assayed for DA, DOPAC, and HVA by HPLC–EC. The HPLC system consisted of an ESA 540 autosampler, an ESA 580 solvent delivery system, an ESA small bore column (MD-150/RP-C18; diameter=3.0 μm) and an ESA Coulochem II electrochemical detector with a working electrode set at a potential of 250 mV with respect to a reference electrode. The mobile phase was purchased from ESA (MD-TM) and consisted of 0.075 μM sodium dihydrogen phosphate, monohydrate, 0.0017 μM 1-octanesulfonic acid, 25 μM EDTA in 10% HPLC grade acetonitrile, and was adjusted to pH=3 with phosphoric acid. The flow rate was set at 0.53 ml/min. Chromatograms were integrated using Hewlett Packard ChemStation software.

2.9. Cocaine assay

COC, BE and NorCOC concentrations were determined directly in dialysate, with no extraction or purification steps or internal standard, by HPLC with UV detection. The HPLC system consisted of a Hewlett-Packard series 1050 solvent delivery system, a Spherisorb regular bore column (diameter=3.0 μm) and a Hewlett-Packard UV detector (Series 1100) with the UV lamp set at 235 nm. The mobile phase consisted of 0.1 M KH_2PO_4 , 5 mM triethylamine in 25% acetonitrile, and was adjusted to pH=3 with phosphoric acid. The flow rate was set at 1.4 ml/min. Chromatograms were integrated using Hewlett Packard ChemStation software.

2.10. Statistical analysis

Behavioural data were examined by ANOVA for chronic treatment (SAL vs. COC), injection number (1–5), pretreatment (18-MC vs. VEH), time (18 intervals of 10 min) and dose. The latter factor had four levels in the locomotor activity experiment (0, 10, 20 and 40 mg/kg) and two levels in the stereotypy experiment (20 and 40 mg/kg). Baseline concentrations of catecholamines were expressed as pmoles/10 μl for analysis of baseline catecholamine content. Catecholamine data following COC administration were expressed as percent of baseline (mean of six baseline samples) and examined by ANOVA for chronic treatment,

pretreatment, and time (15 intervals of 20 min). If there were significant effects, data were decomposed and Duncan Multiple Range post-hoc tests were performed (Statistica).

3. Results

3.1. Locomotor activity

3.1.1. Chronic treatment

As depicted in Fig. 1 (insert), the total amount of locomotor activity expressed by either chronic treatment group during the 30 min SAL sessions habituated across injections [$F(\text{Injection Number})(4,368)=101.64$, $P<0.0001$; post-hoc tests]. Although the locomotor responses to SAL of the two chronic treatment groups did not differ on injection 1, chronic COC treated rats displayed higher locomotor responding to SAL on injections 2, 4 and 5, compared to their chronic SAL counterparts [$F(\text{Chronic Treatment by Injection Number})(4,368)=4.39$, $P<0.002$; post-hoc tests]. This indicated that conditioned locomotion developed in the chronic COC rats with repeated COC exposure. As can be observed in Fig. 1 (main), compared to injection 1 of COC treatment, chronic COC treated rats displayed sensitized levels of total locomotor activity on injections 2–5 of COC treatment [$F(\text{Chronic Treatment})(1,92)=271.07$, $P<0.0001$; $F(\text{Chronic Treatment by Injection Number})(4,368)=7.60$, $P<0.0001$; post-hoc tests].

3.1.2. Dose–response test

As depicted in Fig. 2 (top), chronic COC treated rats displayed higher levels of total locomotion activity in response to SAL during the 30 min pre-test habituation, compared to chronic SAL treated animals [$F(\text{Chronic Treatment})(1,90)=6.46$, $P<0.02$]. 18-MC pretreatment (40 mg/kg, 18.5 h earlier) did not alter the locomotor responses of either Chronic Treatment group during the 30 min pre-test habituation session (no main effect or interaction with Pretreatment, $P>0.05$). These findings indicate that 18-MC did not alter the expression of conditioned locomotion produced by chronic COC administration. To confirm that chronic COC administration produced locomotor sensitization in the VEH rats, the dose–response functions for the two VEH pretreated groups were compared (Fig. 2, open symbols). The dose–response curve for COC-induced locomotion was shifted to the left in chronic COC animals, compared to chronic SAL [$F(\text{Chronic Treatment by Dose})(3,38)=2.78$, $P=0.05$; post-hoc tests]. This finding indicates that the expression of COC-induced locomotor sensitization also persisted during the 2 week period of COC abstinence. Maximum locomotor responding was observed at the 40 mg/kg COC dose in the chronic SAL group [$F(\text{Dose})(3,19)=11.93$, $P<0.0002$; post-hoc tests], whereas maximum locomotor responding

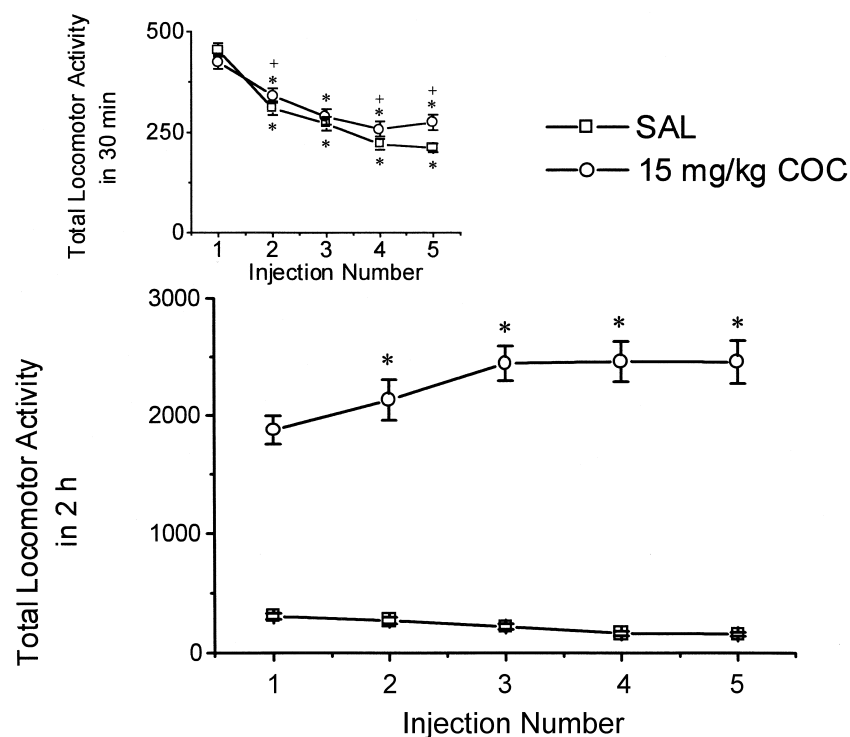


Fig. 1. Main figure. Total locomotor response in 2 h of animals treated daily with either SAL (squares) or 15 mg/kg COC IP (circles). Insert. Total locomotor response of the two chronic treatment groups during the 30 min SAL habituation sessions which preceded each daily treatment injection. Each point represents the mean number of beam breaks ($\pm$ S.E.M.) of 42 rats for the times indicated. * $P < 0.05$, compared to the first injection; + $P < 0.05$, compared to chronic SAL (Duncan Multiple Range post-hoc tests).

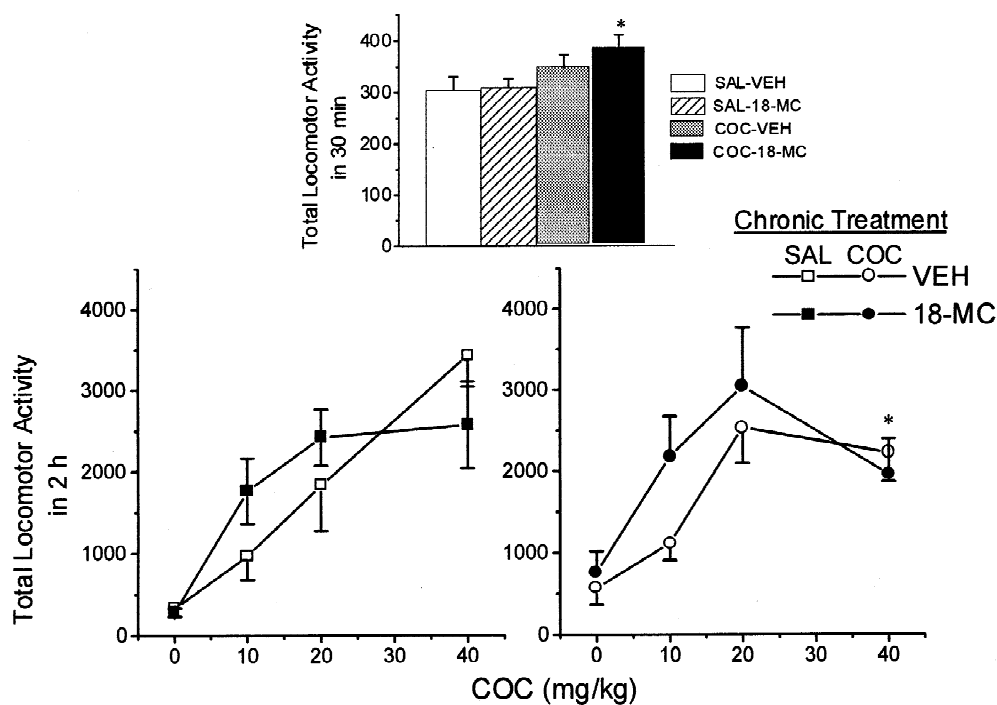


Fig. 2. Main figure. Composite of the effects of 18-MC (40 mg/kg IP, 19 h earlier; closed symbols) or VEH (open symbols) pretreatment on the dose-response curve for total locomotion induced by COC (0, 10, 20, 40 mg/kg IP) in animals treated chronically with either SAL (left) or COC (5 $\times$ 15 mg/kg IP, daily; right). Data represents the mean number of beam breaks ($\pm$ S.E.M.) of 5–6 rats in 2 h. Insert. Effects of 18-MC (40 mg/kg IP, 18.5 h earlier) on the locomotor response to SAL during the pre-test habituation sessions. Each bar represents the mean number of beam breaks 30 min ($\pm$ S.E.M.) of 11–12 animals. * $P < 0.05$, compared to respective chronic SAL (Duncan Multiple Range post-hoc tests).

was observed at the 20 mg/kg COC dose in the chronic COC group [$F(\text{Dose})(3,19)=7.82$, $P<0.002$; post-hoc tests], indicating that chronic COC treatment increased the potency of COC to elicit locomotor activation in VEH pretreated rats.

As can be observed in Fig. 2 (main), in both chronic treatment groups, the effect of 18-MC (40 mg/kg, 19 h earlier) on the overall relationship between COC dose and total locomotor responding to COC was marginal [$F(\text{Pre-treatment by Dose})(3,78)=2.55$, $P=0.06$]. However, as can be observed from Fig. 3, 18-MC significantly altered the timecourse of COC-induced locomotion overall [$F(\text{Pre-treatment by Dose by Time})(33,858)=1.65$, $P<0.02$]. Interestingly, the effect of 18-MC on the timecourse of COC-induced locomotion depended on the previous COC history of the animal [$F(\text{Chronic Treatment by pretreatment by time})(11,858)=1.75$, $P=0.05$]. As depicted in Fig. 3, 18-MC pretreatment increased the early locomotor-activating effects of COC in rats with previous COC experience [$F(\text{Pre-treatment by Dose by Time})(44,1056)=$

1.35, $P=0.06$], without altering the timecourse of acute COC-induced locomotion [$F(\text{Pre-treatment by Dose by Time})(44,1056)=1.28$, $P=0.11$]. Thus, the present findings extend previous reports for IBO [44,45] by demonstrating that chronic COC administration increases the sensitivity to the locomotor-enhancing effects of the synthetic IBO derivative, 18-MC.

3.2. Stereotypy

3.2.1. Chronic Treatment

As depicted in Fig. 4 (main), chronic COC administration (five once daily injections of 15 mg/kg) induced a sensitization of stereotypic behaviour which was expressed by chronic COC rats on injection 5 of chronic treatment [$F(\text{Chronic Treatment})(1,46)=79.88$, $P<0.00001$; $F(\text{Chronic Treatment} \times \text{Injection Number})(4,184)=8.92$, $P<0.00001$; post-hoc tests]. In contrast, the responses to repeated SAL during the 30 min sessions habituated across the five injections in a virtually identical manner in both

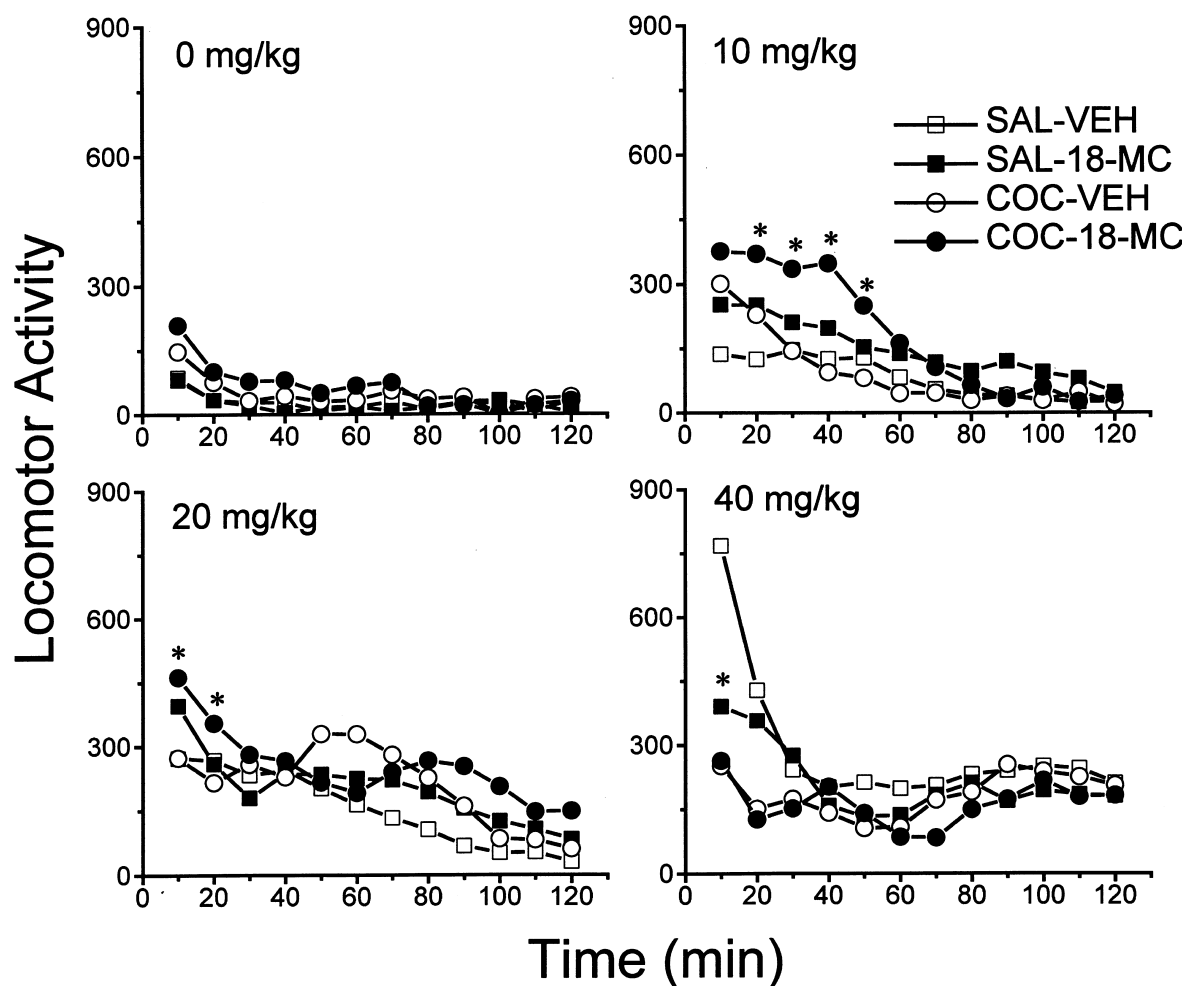


Fig. 3. Effect of pretreatment with either 18-MC (40 mg/kg, 19 h earlier; solid) or VEH (open) on the time-course of locomotion in response to the various test doses of COC (0, 10, 20 or 40 mg/kg) during the 2 h test session in rats treated chronically with either COC (5×15 mg/kg; circles) or SAL (squares). Error bars were omitted for clarity. Each data point represents the mean score of 5–6 rats at the indicated times after COC. * $P<0.05$, compared to respective VEH (Duncan Multiple Range post-hoc tests).

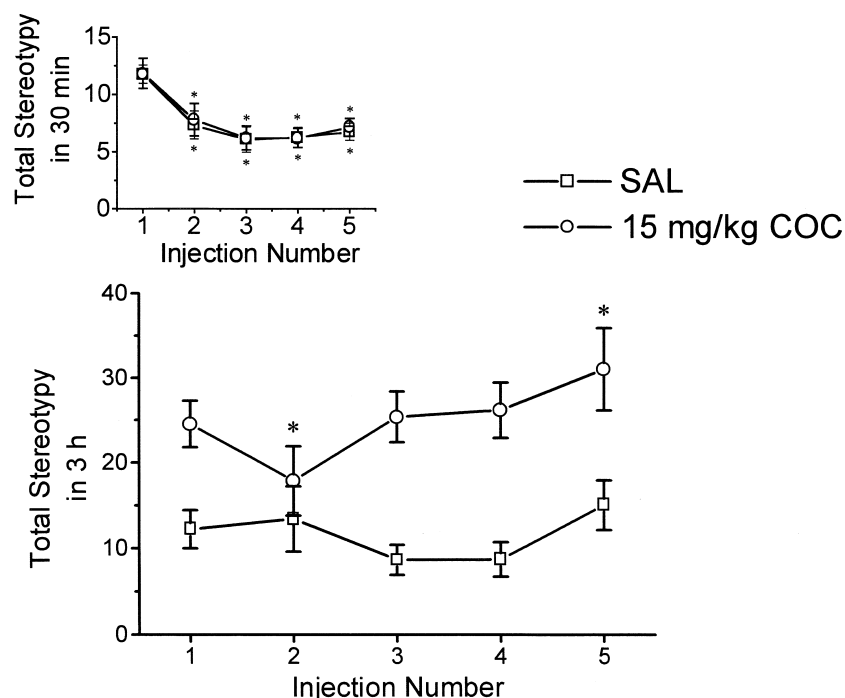


Fig. 4. Main figure. Total stereotypic response in 2 h of animals treated daily with either SAL (squares) or 15 mg/kg COC IP (circles). Insert. Total locomotor response of the two chronic treatment groups during the 30 min SAL habituation sessions which preceded each daily treatment injection. Each point represents the mean total stereotypy score ($\pm$ S.E.M.) of 24 rats for the times indicated. * $P < 0.05$, compared to the first injection (Duncan Multiple Range post-hoc tests).

chronic treatment groups [$F(\text{Injection Number})(4,184) = 50.18$, $P < 0.00001$; no main effects or interactions with Chronic Treatment, $P > 0.05$] (Fig. 4, insert).

Consistent with the results from the chronic treatment phase of the experiment, the stereotypic response to SAL during the 30 min pretest habituation session did not differ as a function of previous COC treatment [$F(\text{Chronic Treatment})$ and $F(\text{Chronic Treatment by time})$, $P > 0.05$]. Compared to VEH pretreated rats, pretreatment with 18-MC (40 mg/kg, 19 h earlier) selectively decreased the expression of stereotypy during the pretest habituation session in rats with previous COC experience [$F(\text{Pretreatment})(1,44) = 4.84$, $P < 0.04$; $F(\text{Chronic Treatment by Pretreatment})(1,44) = 4.84$, $P < 0.04$; post-hoc tests] (Fig. 5, insert).

3.2.2. Test for sensitization

Fig. 5 (main) and Fig. 6 depict, respectively, the total amount of stereotypy and the timecourse of stereotypy expressed by the groups in response to the two test injections of COC (20 and 40 mg/kg). Overall, COC induced dose-dependent increases in the expression of stereotypy [$F(\text{Dose})(1,40) = 57.00$, $P < 0.00001$; $F(\text{Dose by Time})(9,360) = 3.51$, $P < 0.0005$]. In VEH-pretreated rats, repeated COC administration induced a slight sensitization of stereotypy in response to the test injections of COC [$F(\text{Chronic Treatment by Time})(9,180) = 2.14$, $P < 0.03$]; VEH rats with previous COC experience displayed higher

levels of stereotypy during the early portion of the testing session in response to either COC dose, compared to VEH rats receiving COC for the first time (post-hoc tests). Pretreatment with 18-MC potentiated the total amount of stereotypy induced by COC, compared to VEH controls [$F(\text{Pretreatment})(1,40) = 57.00$, $P < 0.0001$] and this effect depended upon the dose of COC administered [$F(\text{Pretreatment by Dose})(1,40) = 5.53$, $P < 0.03$], but not on the previous COC experience of the rat [$F(\text{Pretreatment by Chronic Treatment})$ and $F(\text{Pretreatment by Chronic Treatment by Time})$, $P > 0.05$]. Compared to VEH controls, 18-MC significantly increased the amount of stereotypy expressed in response to 40 mg/kg COC [for 20 mg/kg: $F(\text{Pretreatment})$, $P > 0.05$; for 40 mg/kg COC: $F(\text{Pretreatment})(1,20) = 10.88$, $P < 0.005$] and marginally prolonged the duration of COC's stereotypic activating effects [$F(\text{Pretreatment by Time})(9,180) = 1.86$, $P = 0.06$]. Thus, it appears that the lowered locomotor response observed for 18-MC pretreated rats in the locomotor experiment can be attributed to a potentiation of the stereotypic effects of COC at higher COC doses.

3.3. In vivo microdialysis

3.3.1. Baseline catecholamine content

The average basal concentrations of DA, or either of its two metabolites, DOPAC and HVA, did not differ as a consequence of either chronic COC treatment (five once

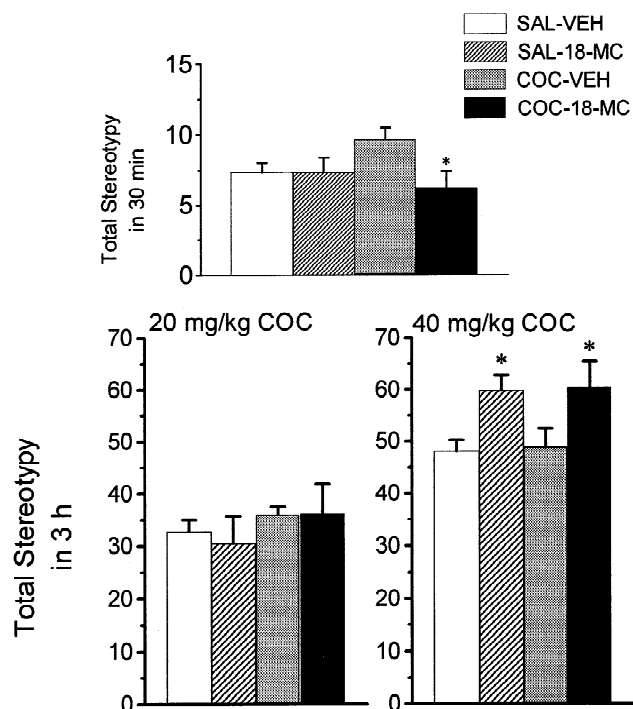


Fig. 5. Main figure. Effects of pretreatment (19 h earlier) with either 18-MC (40 mg/kg, IP; solid) or VEH (open) on the total amount of stereotypy expressed in response to a challenge injection of either 20 or 40 mg/kg COC (left and right, respectively) during the 3 h test session. Each bar represents the mean total stereotypy score ($\pm$ S.E.M.) of 6 rats. Insert. Effects of pretreatment (18.5 h earlier) with either 18-MC (solid) or VEH (open) on the total stereotypy expressed during the 30 min SAL habituation session preceding the COC challenge. Each bar represents the mean total stereotypy score ($\pm$ S.E.M.) of 12 rats. * $P<0.05$, compared to respective VEH (Duncan Multiple Range post-hoc tests).

Table 2

Effects of 18-MC (40 mg/kg, 19 h earlier) or VEH on the basal levels of DA and its metabolites, DOPAC and HVA of rats treated chronically with either COC (5 $\times$ 15 mg/kg) or SAL. Data is expressed as pmoles/10 μ l (mean $\pm$ S.E.M.)

	Chronic SAL		Chronic COC	
	VEH (n=7)	18-MC (n=6)	VEH (n=5)	18-MC (n=7)
DA	0.006 $\pm$ 0.003	0.008 $\pm$ 0.001	0.004 $\pm$ 0.001	0.004 $\pm$ 0.001
DOPAC	5.308 $\pm$ 1.734	3.400 $\pm$ 0.942	3.626 $\pm$ 0.217	1.135 $\pm$ 0.487
HVA	2.234 $\pm$ 0.371	1.703 $\pm$ 0.455	2.196 $\pm$ 0.247	1.786 $\pm$ 0.765

daily injections of 15 mg/kg, IP) or 18-MC pretreatment (40 mg/kg, 17–19 h earlier) (no main effects or interactions with either Chronic Treatment or Pretreatment, $P>0.05$) (Table 2).

3.3.2. Test for sensitization of catecholamines

Consistent with the above behavioural studies, in VEH pretreated rats, chronic COC administration produced a sensitization of extracellular DA levels in the NAC in response to a challenge injection of COC (20 mg/kg), compared to chronic SAL controls [$F(\text{Chronic Treatment by Time})(14,126)=5.52$, $P<0.0001$]. No differences in either DOPAC or HVA levels were observed between the two vehicle-pretreated controls [no main effects or interactions with Chronic Treatment, $P>0.05$]. Compared to VEH pretreated animals, 18-MC pretreatment (40 mg/kg, 19 h earlier) differentially altered the DA response in the NAC to COC, depending on the previous COC history of the animals [$F(\text{Chronic Treatment by Pretreatment by Time})(14,252)=3.52$, $P<0.0001$]. As can be observed in

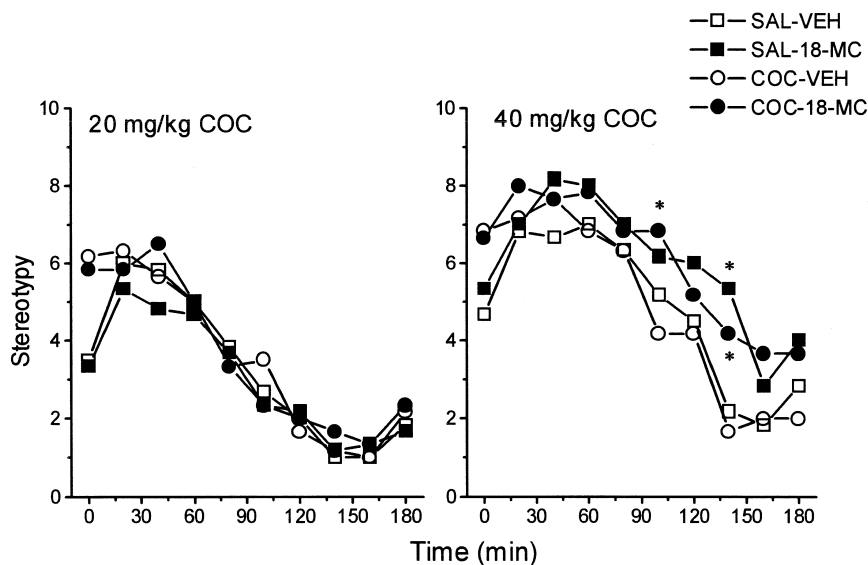


Fig. 6. Effect of pretreatment with either 18-MC (40 mg/kg, 19 h earlier; solid) or VEH (open) on the time-course of stereotypy in response to 20 or 40 mg/kg COC during the 3-h test session in rats treated chronically with either COC (5 $\times$ 15 mg/kg; circles) or SAL (squares). Error bars were omitted for clarity. Each data point represents the mean score ($\pm$ S.E.M.) of 6 rats at the indicated times after COC. * $P<0.05$, compared to respective VEH (Duncan Multiple Range post-hoc tests).

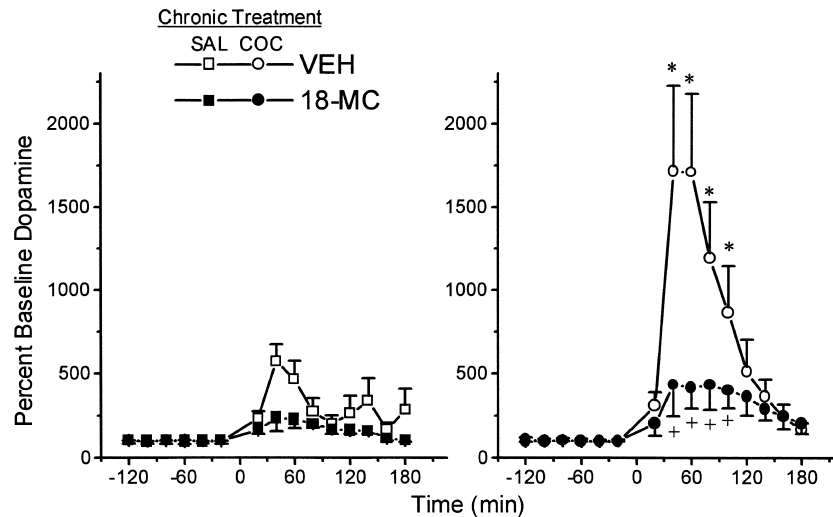


Fig. 7. Effects of 18-MC (40 mg/kg, 19 h earlier; solid) or VEH (open) on the timecourse of extracellular DA in the NAC of rats treated chronically with either COC (5×15 mg/kg; right) or SAL (left) in response to a challenge injection of COC (20 mg/kg). Each data point represents the mean percent of baseline ($\pm$ S.E.M.) of 5–7 rats at the indicated times during testing. * P <0.05 vs. respective chronic SAL; + P <0.05 vs. respective VEH (Duncan Multiple Range post-hoc tests).

Fig. 7 (right), 18-MC pretreatment completely abolished the sensitized DA response to COC [F (Pretreatment by Time)(14, 112)=4.8, P <0.0001; post-hoc tests]. In contrast, 18-MC produced a marginal effect on the DA response in the NAC in chronic SAL rats [F (Pretreatment by Time)(14, 140)=1.71, P =0.06]. Similarly, 18-MC pretreatment differentially altered the DOPAC response to COC, depending on the previous COC history of the rats [F (Chronic Treatment by Pretreatment by Time)(14,266)=1.73, P <0.05]. Consistent with the DA data, compared to VEH controls, 18-MC pretreatment significantly decreased extracellular DOPAC levels in chronic COC treated rats [F (Pretreatment by Time)(14, 112)=4.9, P <0.0001; post-hoc tests], without altering the DOPAC levels of acutely treated animals [F (Pretreatment by Time)(14, 154)=0.66, P =0.81 (Fig. 8, top). As depicted in Fig. 8 (bottom), 18-MC pretreatment did not affect the COC-induced changes in extracellular levels of HVA in either of the chronic treatment groups (no main effects or interactions with Pretreatment, P >0.05). The present findings for acute COC corroborate the results of a previous microdialysis study [23] by demonstrating that 18-MC pretreatment does not produce any statistically significant effect on acute COC-induced changes in DA transmission.

3.3.3. COC assay

Analysis of the area under the curve (AUC) for VEH pretreated rats demonstrated no statistically significant differences in the extracellular concentrations of COC or its metabolites, BE and NorCOC, between rats treated chronically with either COC or SAL [no main effects or interactions with Chronic Treatment, P >0.05] (Fig. 9). Thus, the present results are inconsistent with previous studies [14,33,37] in that chronic COC administration did

not elevate brain COC levels, compared to chronic SAL controls. As is apparent from Fig. 9, 18-MC did not influence the extracellular concentrations of COC or its metabolites, BE and NorCOC, in either chronic treatment group (no main effects or interactions with Pretreatment, P >0.05).

3.3.4. Stereotypy during microdialysis

Consistent with the neurochemical data, in VEH-pretreated rats, chronic COC administration produced a sensitization of stereotypic behaviour in response to COC (20 mg/kg) [F (Chronic Treatment by Time)(12,132)=5.00, P <0.0001]. As depicted in Fig. 10, in contrast to the neurochemical and COC metabolism data, 18-MC (40 mg/kg, 19 h earlier) enhanced the stereotypic responses of the rats during the microdialysis session [F (Pretreatment by Time)(12,252)=3.50, P <0.0001; post-hoc tests]. In chronic SAL treated rats, 18-MC increased both the maximum effect and the duration of COC-induced stereotypy [F (Pretreatment by Time)(12,132)=5.00, P <0.0001; post-hoc tests]. Although, no statistically significant interaction between Pretreatment and Time was apparent in chronic COC treated rats [F (12,120)=1.08, P >0.05], decomposition of the Time effect in chronic COC rats [F (12,120)=23.53, P <0.0001] indicated that 18-MC pretreated rats displayed a more prolonged duration of sensitized levels of stereotypy, compared to VEH controls [COC–VEH: F (Time)(12, 48)=10.89, P <0.0001; for COC–18-MC: F (12,72)=15.45, P <0.0001; post-hoc tests]. Thus, the present results demonstrate that the enhancing effects of 18-MC on COC-induced behaviour appear to be dissociated from its effects on COC-induced changes in DA transmission in the NAC and COC metabolism.

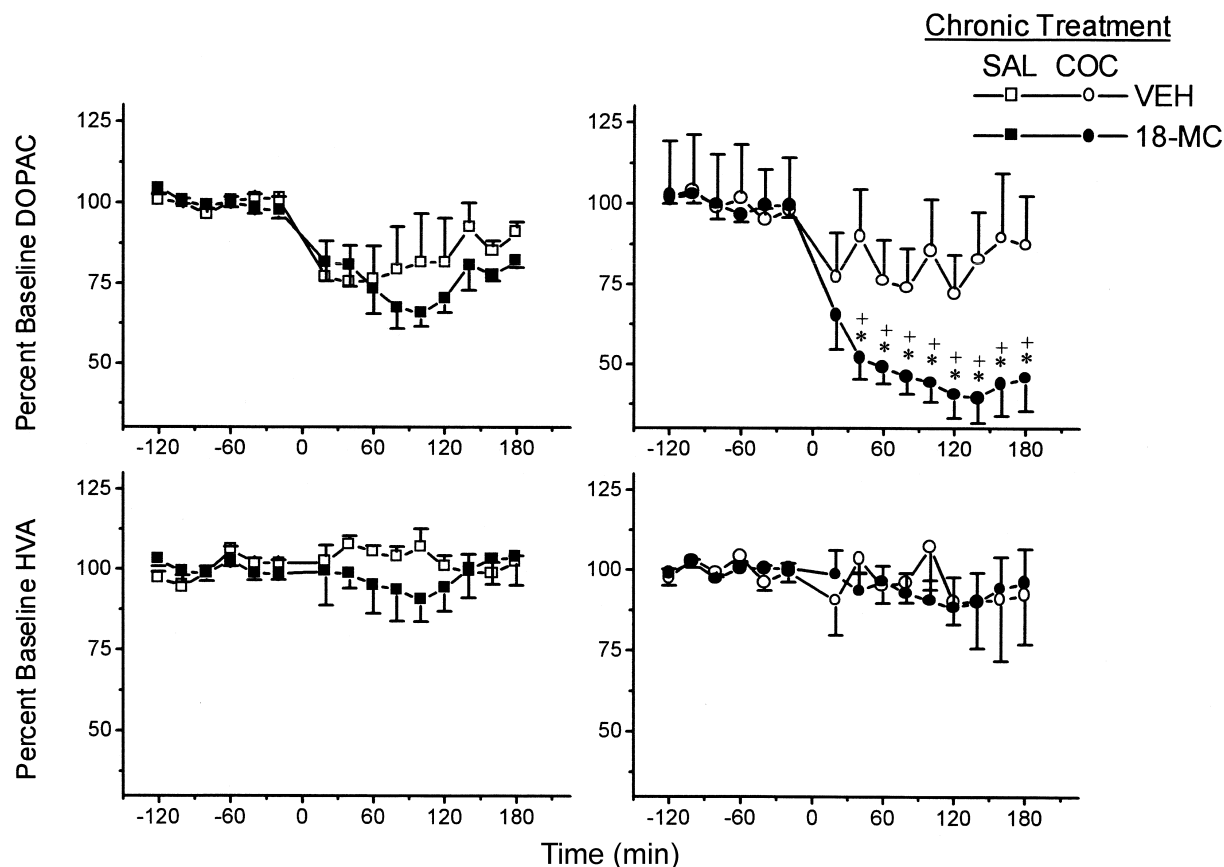


Fig. 8. Comparison of the effects of 18-MC (solid) or VEH (open) on the extracellular levels of DOPAC (top) and HVA (bottom) of rats treated chronically with either COC (5×15 mg/kg; right) or SAL (left) in response to a challenge injection of COC (20 mg/kg). Each data point represents the mean percent of baseline ($\pm$ S.E.M.) of 5–7 rats at the indicated times during testing. * $P < 0.05$ vs. respective chronic SAL; + $P < 0.05$ vs. respective VEH (Duncan Multiple Range post-hoc tests).

4. Discussion

The present study was conducted to determine the effects of a potential anti-addictive agent, 18-MC, on the expression of motor behavioural and DA sensitization following the repeated administration of the psychomotor stimulant, COC. The principal rationale for conducting this study relates to the theoretical implication for a role of sensitization in the development and expression/maintenance of drug addicted behaviours (e.g. [26,39] but see [12,18]). We hypothesized that if drug addicted behaviours reflect the expression of drug-induced sensitization, this expression should be attenuated by compounds that block the self-administration of drugs in laboratory animals (e.g., 18-MC; for reviews [21,22]) and/or are anti-addictive in humans (e.g., IBO [17,40]). Furthermore, given the putative association between the sensitization of motor behaviour and the sensitization of mesolimbic DA transmission (e.g. [27,38]), we hypothesized that the effects of *iboga* pretreatment on the expression of DA sensitization would be coincident with their effects on the expression of motor sensitization. Inconsistent with these hypotheses, pretreatment with the novel, synthetic *iboga* alkaloid

congener, 18-MC, potentiated the expression of motor activation and sensitization to COC and did not alter significantly the DA response to an acute injection of COC in the NAC. However, consistent with these hypotheses, 18-MC pretreatment blocked the expression of DA sensitization in the NAC of rats with repeated COC experience.

To reconcile the dissociation between the effects of COC on motor behaviour and the effect of COC on reinforcing processes (e.g. [30,32,44–46]), it was proposed that *iboga* agents exert their anti-addictive effects via an increase in the aversiveness of stimulant drugs (e.g. [30,32]) and that this effect is greater in individuals with previous stimulant experience (e.g. [44]). This suggestion was based on evidence implicating psychomotor activation in the mediation of not only the positive reinforcing effects of stimulant drugs (e.g. [13,29]), but also their aversive properties (e.g. [8]). In support of this position, IBO enhances the DA response to an acute injection of either COC or amphetamine [30,31]. However, recent microdialysis findings for both acute and chronic COC-treated rats provide evidence against our increased sensitivity hypothesis. First, 18-MC pretreatment does not produce any statistically significant effect on the acute DA response

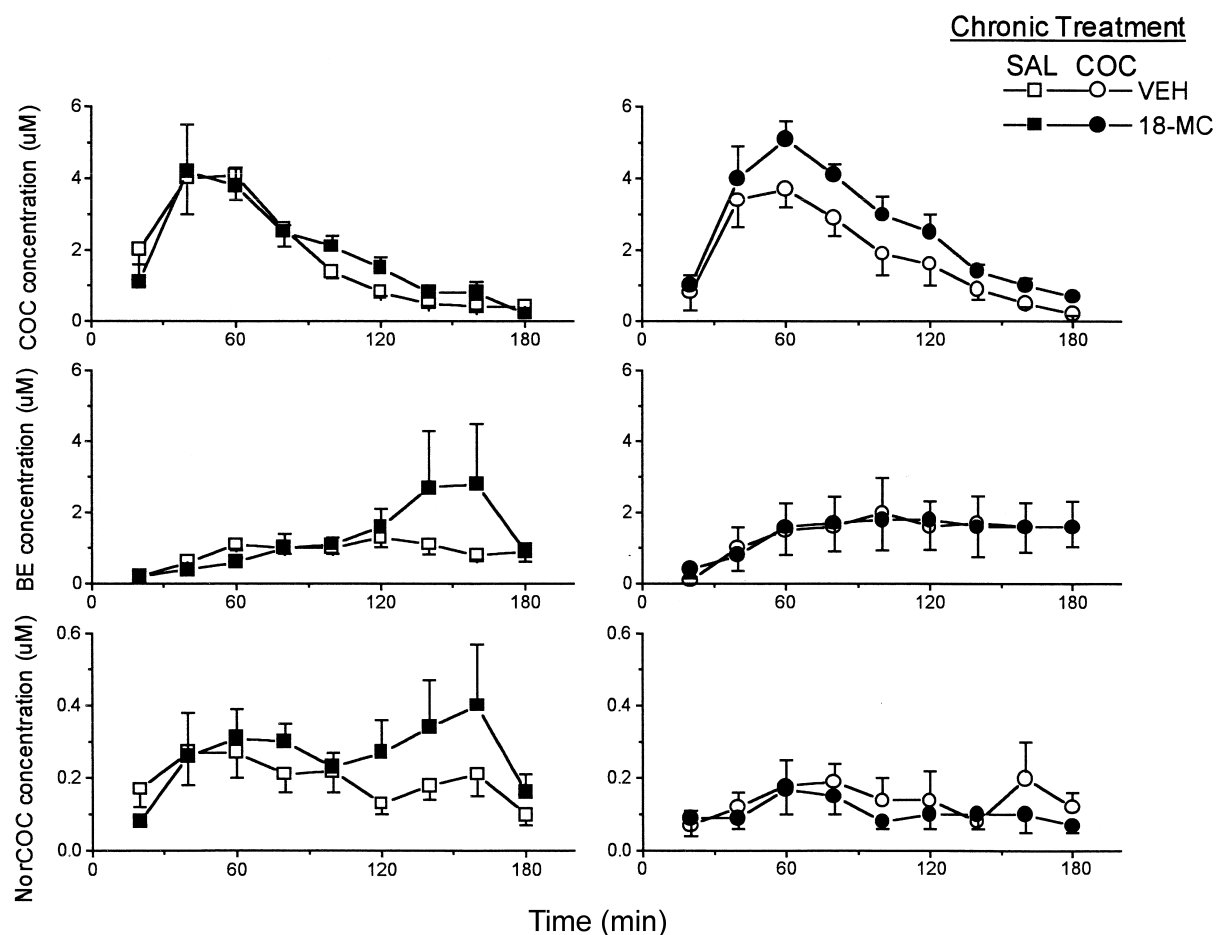


Fig. 9. Effects of 18-MC (40 mg/kg, 19 h earlier; solid) or VEH (open) on the timecourse of brain levels of COC (top), BE (middle) and NorCOC (bottom) following COC administration (20 mg/kg) in rats treated chronically with either COC (5 $\times$ 15 mg/kg; circles) or SAL (squares). Each data point represents the mean concentration ($\pm$ S.E.M.) of 6–8 rats at the indicated times following COC. * $P < 0.05$ vs. first respective sample (Duncan's Multiple Range post-hoc tests).

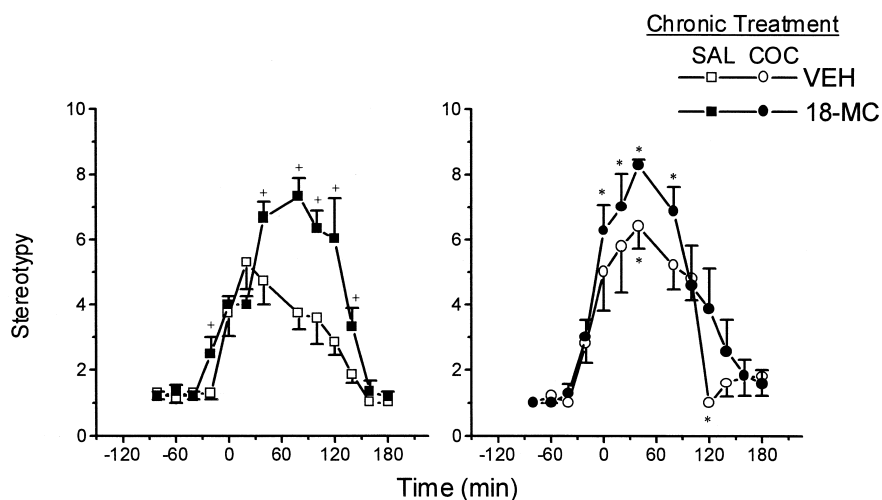


Fig. 10. Comparison of the effects of 18-MC (40 mg/kg, 19 h earlier; solid) or VEH (open) on the timecourse of stereotypy expressed during the microdialysis study by rats treated chronically with either COC (5 $\times$ 15 mg/kg; right) or SAL (left). Each data point represents the stereotypy score ($\pm$ S.E.M.) of 6–8 rats at the indicated times during testing. * $P < 0.05$ vs. respective chronic SAL; + $P < 0.05$ vs. respective VEH (Duncan Multiple Range post-hoc tests).

to COC ([21]; present study). Secondly, both 18-MC [present study] and IBO [56] block the expression of DA sensitization in the NAC. Thus, it appears that the effects of COC on motor behaviour can be dissociated from the effects of COC on both extracellular levels of DA and reinforcing processes. Interestingly, the effects of 18-MC on DA sensitization are related to the effects of 18-MC on COC-induced reinforcement. These findings are consistent with previous results for morphine [48] and imply that *iboga* pretreatment can reverse the neuroadaptations in the mesolimbic DA system produced by repeated COC administration and that this mechanism may underlie the putative anti-addictive effects of *iboga* agents.

A recent series of studies conducted by Di Chiara and colleagues demonstrated that the expression of behavioural sensitization to morphine [6], nicotine [5], amphetamine and COC [7] are coincident with a sensitization of DA levels in the core of the NAC. A challenge injection of COC and nicotine administration produced a reduction in DA levels in the shell of the NAC, and this was coincident with the expression of behavioural sensitization to these drugs [5–7]. The present results for 18-MC pretreated rats are consistent with this latter finding; the magnitude of the behavioural response to COC did not correspond with that of the DA response in the shell of the NAC. In repeated COC treated rats, these effects were, in fact, opposite. Thus, as recently proposed for IBO [56], 18-MC might exert its potentiating effects on behavioural sensitization by blocking the increase in DA responsiveness in the shell of the NAC that serves normally to counteract the sensitization of core DA responsiveness. The corollary of this hypothesis is that 18-MC exerts its effects on the expression of COC-induced motor sensitization by altering DA sensitization in the core of the NAC. In support of this, IBO pretreatment enhanced the DA response to stimulant drugs in previous microdialysis studies in which the microdialysis probes were placed predominantly in the core of the NAC [30,31]. However, it should be noted that no effect of 18-MC pretreatment was observed on extracellular levels of DA in the dorsolateral striatum [21], a brain region with similar anatomical connectivity (e.g. [24,55]) and presumably function [54] as the core of the NAC.

There are a number of past [21,48] and present results from our laboratory that contrast directly with those of Cadoni and colleagues [5–7]. First, in our hands, the chronic administration of drugs of abuse produces a sensitization of DA responsiveness in the shell of the NAC ([48,56]; present study). Although the robustness of the expression of COC-induced behavioural sensitization varies between studies (e.g. [44] vs. present study for COC-induced locomotion), we consistently observe that the expression of COC-induced behaviour and COC-induced behavioural sensitization is coincident temporally with the expression of DA sensitization in the shell of the NAC ([21,56]; present study). No reduction in the DA response in the shell of the NAC to COC has ever been observed in

this laboratory in any of the chronic drug treated groups tested to date, regardless of *iboga* pretreatment ([56]; present study). For example, although 18-MC pretreatment blocks the expression of DA sensitization to COC, it does not lower the levels of DA below baseline. Two possibilities may account for the differences between the two laboratories. The first relates to differences in the placement of the microdialysis probes in the shell of the NAC; Di Chiara and colleagues use a placement that is more anterior to that used by our laboratory (e.g., +2.0–2.2 mm vs. +1.6 mm from bregma, respectively). However, this possibility does not seem likely given that the DA response to both peripherally and centrally administered stimulant drugs appears to be greater in the more rostral portions of the NAC shell, compared to the more mediocaudal aspects (e.g. [23]). The second possibility relates to differences in the time of surgery with respect to the repeated COC administration; in our studies, surgeries were performed prior to COC treatment, whereas Cadoni et al. [7] conducted their surgeries 10–14 days following the cessation of COC treatment. Thus, the possibility exists that the stress from the surgery facilitated the induction of DA sensitization in our studies [27,42]. Alternatively, it may be argued that, in the study by Cadoni et al. [7], the non-specific depressive effects of surgery disrupted the expression of sensitization.

Several laboratories have demonstrated that chronic drug self-administration can induce the expression of behavioural and/or neurochemical sensitization (e.g. [10,11,15,36]) and theories have implicated the phenomenon of DA sensitization in the mediation of drug reward/reinforcement, drug-seeking behaviour and relapse to addiction (e.g. [26,39] but see [12,18]). The evidence to date indicates that the “therapeutic” effects of *iboga* agents involve a reversal of DA sensitization in the shell of the NAC. Consistent with their ability to attenuate the self-administration of a variety of drugs of abuse, IBO or 18-MC block the expression of DA sensitization in the shell of the NAC in rats treated repeatedly with both opiates [48] or stimulants ([56]; present study). Given the putative role for mesolimbic DA transmission in the mediation of the appetitive, rewarding/reinforcing or incentive motivational effects of both stimulant and opiate drugs, the ability of *iboga* agents to consistently block the DAergic consequences of repeated drug treatment raises the possibility that *iboga* agents attenuate drug self-administration by resetting the neuroadaptations in the mesolimbic DA system produced by repeated drug administration. The repeated administration of both stimulants and opiates can up- or downregulate the expression of number of receptors for which *iboga* agents show moderate binding affinity (for receptor bindings profiles [21,22]). These include the NMDA subtype of glutamate receptor, and the mu and kappa subtypes of opiate receptor (e.g. [1,2,49–51,53]). As activation of these receptors can modulate DA release (e.g. [27]), it is proposed that *iboga*

pretreatment blocks DA sensitization by reversing the receptor adaptations produced by chronic drug administration. This hypothesis is currently under investigation by our laboratory.

In summary, the present study demonstrated that the effects of pretreatment with the synthetic *iboga* alkaloid congener and potential anti-addictive drug, 18-MC (40 mg/kg, 19 h earlier), differentially alters the motor and neurochemical responses to COC. In both acute and chronic COC-treated rats, 18-MC enhances COC-induced locomotion and stereotypy; in contrast, 18-MC does not affect and decreases, respectively, the increase in NAC DA levels of rats treated acutely and chronically with COC. None of the effects of 18-MC observed in the present study appear to be related to alterations in brain penetration of COC or COC metabolism. Given the putative role for the sensitization of DA transmission in the NAC in mediating various aspects of drug addiction, the present results support our previous suggestion [48,56] that the potential anti-addictive efficacy of 18-MC might be related to an ability to restore normal functioning to a hyper-sensitive mesolimbic DA system, whereby reversing the pathological psychobiological consequences of repeated drug administration.

Acknowledgements

This study was supported by NIDA grant DA 03817.

References

- [1] A.V. Azaryan, B.J. Clock, J.G. Rosenberger, B.M. Cox, Transient upregulation of μ opioid receptor mRNA levels in nucleus accumbens during chronic cocaine administration, *Can. J. Physiol. Pharmacol.* 76 (1998) 278–283.
- [2] H.N. Bhargava, S. Kumar, Sensitization to the locomotor stimulant effect of cocaine modifies the binding of [3H]MK-801 to brain regions and spinal cord of the mouse, *Gen. Pharmacol.* 32 (1999) 359–363.
- [3] K.C. Berridge, T.E. Robinson, What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?, *Brain Res. Rev.* 28 (1998) 309–369.
- [4] J.R. Blackburn, K.K. Szumlinski, Ibogaine effects on sweet preference and amphetamine-induced locomotion: Implications for drug addiction, *Behav. Brain Res.* 89 (1997) 99–106.
- [5] C. Cadoni, G. Di Chiara, Differential changes in accumbens shell and core dopamine in behavioral sensitization to nicotine, *Eur. J. Pharmacol.* 387 (2000) R23–25.
- [6] C. Cadoni, G. Di Chiara, Reciprocal changes in dopamine responsiveness in the nucleus accumbens shell and core and in the dorsal caudate-putamen in rats sensitized to morphine, *Neuroscience* 90 (1999) 447–455.
- [7] C. Cadoni, M. Solinas, G. Di Chiara, Psychostimulant sensitization: differential changes in accumbal shell and core dopamine, *Eur. J. Pharmacol.* 388 (2000) 69–76.
- [8] S. Cohen, Cocaine, *J. Am. Med. Assoc.* 231 (1972) 74–75.
- [9] V. Deroche, M. Le Moal, P.V. Piazza, Cocaine self-administration increases the incentive motivational properties of the drugs in rats, *Eur. J. Neurosci.* 11 (1999) 2731–2736.
- [10] T.J. De Vries, A.N.M. Schoffeleers, R. Binnekade, A.H. Mulder, L.J.M.J. Vanderschuren, Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization, *Eur. J. Neurosci.* 10 (1998) 3565–3571.
- [11] G. Di Chiara, Drug addiction as dopamine-dependent associative learning disorder, *Eur. J. Pharmacol.* 375 (1999) 13–30.
- [12] F.J. Dunne, Substance misuse in the young, *Br. J. Hosp. Med.* 50 (1993) 643–649.
- [13] V.S. Estevez, B.T. Ho, L.F. Englert, Inhibition of the metabolism of cocaine by SKF-525A, *Res. Commun. Chem. Pathol. Pharmacol.* 17 (1977) 179–182.
- [14] J.L. Falk, F. Ma, C.E. Lau, Chronic oral cocaine self-administration pharmacokinetics and effects on spontaneous and discriminative motor functions, *J. Pharmacol. Exp. Ther.* 257 (1991) 57–465.
- [15] H.C. Fibiger, A.G. Phillips, Reward, motivation, cognition: Psychobiology of mesotelencephalic dopamine systems, in: V.B. Mountcastle, F.E. Bloom, S.R. Geiger (Eds.), *Handbook of physiology: the nervous system*, Vol. 4, American Physiological Society, Bethesda, MD, 1986, pp. 647–675.
- [16] G. Frenken, From the roots up: Ibogaine and addict self-help, in: K.R. Alper, S.D. Glick (Eds.) *The Alkaloids. Ibogaine: Proceedings of an Interdisciplinary Conference*. Academic Press, New York, 2000, in press.
- [17] F.H. Gawin, M.E. Khalsa-Denison, Is craving mood-driven or self-propelled? Sensitization and “street” stimulant addiction, *NIDA Res. Monogr.* 163 (1999) 224–250.
- [18] S.D. Glick, M.E. Kuehne, I.M. Maisonneuve, U.K. Bandarage, H.H. Molinari, 18-methoxycoronaridine, a non-toxic iboga alkaloid congener: effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats, *Brain Res.* 719 (1996) 29–35.
- [19] S.D. Glick, I.M. Maisonneuve, Mechanisms of anti-addictive actions of ibogaine, *Ann. N.Y. Acad. Sci.* 844 (1998) 214–226.
- [20] S.D. Glick, I.M. Maisonneuve, L.B. Hough, M.E. Kuehne, U.K. Bandarage, ($\pm$)-18-Methoxycoronaridine: A novel iboga alkaloid congener having potential anti-addictive efficacy, *CNS Drug Rev.* 5 (1999) 27–42.
- [21] S.D. Glick, I.M. Maisonneuve, K.K. Szumlinski, 18-Methoxycoronaridine (18-MC) and ibogaine: comparison of anti-addictive efficacy, toxicity and mechanisms of action. *Ann. N.Y. Acad. Sci.* (1999), in press.
- [22] C.A. Heidbreder, J. Feldon, Amphetamine-induced neurochemical and locomotor responses are expressed differentially across the anteroposterior axis of the core and shell subterritories of the nucleus accumbens, *Synapse* 29 (1998) 310–322.
- [23] A.L. Jongen-Relo, H.J. Groenewegen, P. Voorn, Evidence for a multi-compartmental histochemical organization of the nucleus accumbens in the rat, *J. Comp. Neurol.* 337 (1993) 267–276.
- [24] P.W. Kalivas, P. Duffy, L.A. DuMars, C. Skinner, Behavioral and neurochemical effects of acute and daily cocaine administration in rats, *J. Pharmacol. Exp. Ther.* 245 (1988) 485–492.
- [25] P.W. Kalivas, R.C. Pierce, J. Cornish, B.A. Sorg, A role for sensitization in craving and relapse in cocaine addiction, *J. Psychopharmacol.* 12 (1998) 49–53.
- [26] P.W. Kalivas, J. Stewart, Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity, *Brain Res. Rev.* 16 (1991) 223–244.
- [27] G.F. Koob, Drugs of abuse: Anatomy, pharmacology and function of reward pathways, *Trends Pharmacol. Sci.* 13 (1992) 177–184.
- [28] J.C. Kramer, Introduction to amphetamine abuse, in: E.H. Ellinwood, S. Cohen (Eds.), *Current Concepts in Amphetamine Abuse*, NIMH, Rockville, MD, 1970, pp. 177–184.
- [29] I.M. Maisonneuve, S.D. Glick, Interactions between ibogaine and cocaine in rats: in vivo microdialysis and motor behavior, *Eur. J. Pharmacol.* 212 (1992) 263–266.

- [31] I.M. Maisonneuve, R.W. Keller Jr., S.D. Glick, Interactions of ibogaine and D-amphetamine: in vivo microdialysis and motor behaviour in rats, *Brain Res.* 579 (1992) 87–92.
- [32] I.M. Maisonneuve, K.E. Visker, G.L. Mann, U.K. Bandarage, M.E. Kuehne, S.D. Glick, Time-dependent interactions between iboga agents and cocaine, *Eur. J. Pharmacol.* 336 (1997) 123–126.
- [33] P.K. Nayak, A.L. Misra, S.J. Mule, Physiological disposition and biotransformation of [3 H]cocaine in acutely and chronically treated rats, *J. Pharmacol. Exp. Ther.* 196 (1976) 556–569.
- [34] G. Paxinos, C. Watson, *The Rat Brain in Stereotaxic Coordinates*, Academic Press, Orlando, FL, 1984.
- [35] S.M. Pearl, D.W. Johnson, S.D. Glick, Prior morphine exposure enhances ibogaine antagonism of morphine-induced locomotor stimulation, *Psychopharmacology* 121 (1995) 470–475.
- [36] A.G. Phillips, P. Di Ciano, Behavioural sensitization is induced by intravenous self-administration of cocaine by rats, *Psychopharmacology* 124 (1996) 279–281.
- [37] M.E.A. Reith, M. Benuck, A. Lajtha, Cocaine disposition in the brain after continuous or intermittent treatment and locomotor stimulation in mice, *J. Pharmacol. Exp. Ther.* 243 (1987) 281–287.
- [38] T.E. Robinson, J.B. Becker, Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis, *Brain Res. Rev.* 11 (1986) 157–198.
- [39] T.E. Robinson, K.C. Berridge, The neural basis of drug craving: an incentive-sensitization theory of drug addiction, *Brain Res. Rev.* 18 (1993) 247–291.
- [40] S.G. Sheppard, A preliminary investigation of ibogaine: case reports and recommendations for further study, *J. Subst. Abuse Treat.* 11 (1994) 379–385.
- [41] J. Stewart, Conditioned stimulus control of the expression of sensitization of the behavioral activating effects of opiate and stimulant drugs, in: I. Gormezano, E.A. Wasserman (Eds.), *Learning and Memory: Behavioral and Biological Substrates*, Lawrence Erlbaum Publishers, Hillsdale, NJ, 1982, pp. 129–151.
- [42] J. Stewart, A. Badiani, Tolerance and sensitization to the behavioral effects of drugs, *Behav. Pharmacol.* 4 (1993) 289–312.
- [43] K.K. Szumlinski, M.Y. Balogun, I.M. Maisonneuve, S.D. Glick, Interactions between iboga agents and methamphetamine sensitization: studies of locomotion and stereotypy in rats, *Psychopharmacology* (2000), in press.
- [44] K.K. Szumlinski, I.M. Maisonneuve, S.D. Glick, Ibogaine enhances the expression of locomotor sensitization in rats chronically treated with cocaine, *Pharmacol. Biochem. Behav.* 63 (1999) 457–464.
- [45] K.K. Szumlinski, I.M. Maisonneuve, S.D. Glick, Pretreatment with the putative anti-addictive drug, ibogaine, increases the potency of cocaine to elicit locomotor responding: a study with acute and chronic cocaine-treated rats, *Psychopharmacology* 145 (1999) 227–233.
- [46] K.K. Szumlinski, I.M. Maisonneuve, S.D. Glick, Iboga agents enhance the expression of cocaine-induced stereotypy in acute and chronic cocaine-treated rats, *Behav. Pharmacol.* 10 (1999) S92.
- [47] K.K. Szumlinski, I.M. Maisonneuve, S.D. Glick, 18-Methoxycoronaridine (18-MC) differentially alters the sensitized behavioural and dopaminergic responses to repeated cocaine and morphine administration: Implications for sensitization in the mediation of drug addiction, *Ann. N.Y. Acad. Sci.* (2000), in press.
- [48] K.K. Szumlinski, I.M. Maisonneuve, S.D. Glick, The potential anti-addictive agent, 18-methoxycoronaridine (18-MC) blocks the sensitized dopamine and locomotor responses produced by repeated morphine treatment, *Brain Res.* 864 (2000) 13–23.
- [49] J. Turchan, B. Przewlocka, W. Lason, R. Przewlocki, Effects of repeated psychomotorstimulant administration on the prodynorphin system activity and kappa opioid receptor density in the rat brain, *Neuroscience* 85 (1998) 1051–1059.
- [50] J. Turchan, B. Przewlocka, G. Toth, W. Lason, A. Borsodi, R. Przewlocki, The effect of repeated administration of morphine, cocaine and ethanol on mu and delta opioid receptor density in the nucleus accumbens and striatum of the rat, *Neuroscience* 91 (1999) 971–977.
- [51] E.M. Unterwald, J.M. Rubinfeld, M.J. Kreek, Repeated cocaine administration upregulates kappa and mu, but not delta, opioid receptors, *Neuroreport* 15 (1994) 1613–1616.
- [52] R.A. Wise, M.A. Bozarth, A psychomotor stimulant theory of addiction, *Psychol. Rev.* 94 (1987) 469–492.
- [53] V. Yuferov, Y. Zhou, R. Spangler, C.E. Maggos, A. Ho, M.J. Kreek, Acute “binge” cocaine increases mu-opioid receptor mRNA levels in areas of the rat mesolimbic mesocortical dopamine system, *Brain Res. Bull.* 48 (1999) 109–112.
- [54] D.S. Zahm, Functional-anatomical implications of the nucleus accumbens core and shell territories, *Ann. N.Y. Acad. Sci.* 877 (1999) 113–128.
- [55] D.S. Zahm, L. Heimer, Specificity in the efferent projections of the nucleus accumbens in the rat: Comparison of the rostral pole projection patterns with those of the core and shell, *J. Comp. Neurol.* 327 (1993) 220–232.
- [56] K.K. Szumlinski, I.M. Maisonneuve, S.D. Glick, Differential effects of ibogaine on behavioural and dopamine sensitization, *Eur. J. Pharmacol.* (2000), in press.